Clinical Investigations

PREVENTION

Syncope in Complex Regional Pain Syndrome

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ABSTRACT

Background: Complex regional pain syndrome (CRPS) is a debilitating pain syndrome characterized clinically by severe pain along with signs and symptoms of autonomic dysfunction. Presyncope and syncope are common in these patients. The purpose of this study was to investigate the cause of these symptoms in these patients.

Hypothesis: Patients with CRPS are more prone to presyncope and syncope as evidenced by head-up tilt table testing (HUTT).

Methods: Patients with CRPS underwent a complete cardiac evaluation that included a 12-lead electrocardiogram, 2-dimensional echocardiography, 24-hour Holter monitoring, and HUTT.

Results: Seventy-four patients with CRPS were evaluated. Eight CRPS patients (10%) could not complete a HUTT due to pain. Of the 66 CRPS patients who completed a HUTT, 15 (37.9%) reported pretest symptoms of presyncope or syncope. Twenty-eight CRPS patients (42.4%) had a positive HUTT. CRPS patients with lower limb involvement were more likely to have vasovagal syncope or orthostasis on HUTT than those with upper extremity or total body involvement (12 of 18 [67%] vs 16 of 48 [33%]; $P = 0.015$).

Conclusions: Syncope is common in patients with CRPS, especially with lower limb involvement. Autonomic dysregulation of the lower extremities leads to impaired sympathetic vasoconstriction and venous pooling, which can predispose these patients to syncope. Physician awareness of this syndrome will lead to improved recognition and treatment of their symptoms of presyncope or syncope.

Introduction

Complex regional pain syndrome (CRPS) is a debilitating pain syndrome characterized by severe pain and signs and symptoms of autonomic dysfunction.[1–3] It is these signs and symptoms of autonomic dysfunction that differentiate CRPS from other chronic pain syndromes. The autonomic signs and symptoms associated with CRPS include changes in skin color and temperature, edema, swelling, and abnormal sweating.[4–6] There is strong evidence to support an etiologic role of the sympathetic nervous system not only as the cause of these specific autonomic signs and symptoms but in CRPS as a whole. Patients with CRPS have been shown to have impaired sympathetic nervous system function, and past studies have shown that sympathetic blockade has relieved the symptoms of CRPS in some patients.[7,8]

CRPS is most often caused by peripheral nerve injury and is not as rare a condition as first believed. It can develop in up to 5% of all nerve injuries and demonstrates a female to male ratio of 3:1.[1,3,9] Although not reported in the literature, our group recognized that many patients with CRPS have symptoms of presyncope and syncope, which may be related to autonomic dysfunction, a cardinal feature of CRPS. The purpose of this study was to investigate the prevalence and cause of presyncope and syncope in patients with CRPS.

Methods

We recruited patients from the neurology clinic at Drexel University College of Medicine from January 2007 to January 2009 who had been diagnosed with CRPS and were being evaluated for treatment with intravenous ketamine. All patients underwent a complete neurological evaluation. The inclusion criteria for ketamine treatment included: (1) ages 18 to 65 years; (2) met the revised 2007 International Association for the Study of Pain criteria for CRPS; and (3) suffered intractable pain for a minimum of 6 months and had failed at least 3 of the following therapies: nonsteroidal anti-inflammatory drugs, antiseizure medications, nonopioid analgesics, opioid analgesics, nerve blocks, antidepressants, muscle relaxants, or physical therapy. The exclusion criteria for ketamine therapy included: (1) pregnant patients; (2) known substance abuse; (3) glaucoma; (4) hyperthyroidism; (5) patients on calcium channel or β - blockers (due to the need to use clonidine with ketamine); and (6) patients with major medical problems including uncontrolled hypertension, cardiac failure, renal failure, or liver failure. Relevant neurological data that

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included pain intensity (numerical rating scale of 0 being no pain and 10 the worst pain imaginable), mechanical and thermal allodynia, hyperalgesia (to pinprick), duration of CRPS, and site of injury were abstracted from the patient records.

Patients who were deemed candidates for intravenous ketamine therapy were then referred for cardiac evaluation. Ketamine has been shown to cause arrhythmias, change in blood pressure, and worsening left ventricular dysfunction in individuals with a history of heart failure.[10] Their cardiac evaluation was part of the routine protocol in screening patients for their ketamine treatments. The study protocol was approved by the Drexel University College of Medicine Institutional Review Board.

All patients underwent a complete history, physical examination, and 12-lead electrocardiogram (ECG) recording. They were specifically asked about symptoms of presyncope or syncope. A 2-dimensional (2-D) echocardiogram was obtained to rule out cardiac dysfunction and structural heart disease. A 24-hour Holter monitor was administered to identify any potential cardiac arrhythmias and to determine time domain heart rate variability. A head-up tilt table test (HUTT) was obtained to evaluate the patient's autonomic function.

HUTTs were performed according to the following protocol. Patients were brought to the cardiac electrophysiology laboratory in a fasting condition between the time of 9 AM and 12 PM. The patients were instructed not to take medications prior to the test. They were connected to continuous electrocardiographic and noninvasive hemodynamic monitoring. Baseline blood pressure and heart rate were recorded after lying in the supine position on the tilt-table for 10 minutes. Patients were then tilted head-up on a motorized tilt table to 70 degrees for 30 minutes. Heart rate, blood pressure, and symptom assessment were recorded every 3 minutes. If syncope did not occur, 400 micrograms of sublingual nitroglycerin was administered as an induction agent with continuation of the test for 20 more minutes. Five patients with CRPS obtained their HUTT at an outside institution, 3 of whom received Isuprel as the provocation agent, and 1 patient refused the nitroglycerin. A positive HUTT was defined as symptoms of presyncope or syncope associated with relative bradycardia and/or hypotension as defined by the Vasovagal Syncope International Study (VASIS).[11] A positive HUTT was further defined as:

> Type 1: mixed. Heart rate (HR) decreases by >10% but does not decrease to <40 bpm for >10 seconds. Blood pressure (BP) falls before HR.
> Type 2A: cardioinhibition witout asystole. Minimum HR <40 bpm for >10 seconds, or asystole occurs for <3 seconds. BP falls before HR.
> Type 2B: cardioinhibition with asystole. Minimum HR <40 bpm for >10 seconds, or asystole occurs for >3 seconds. BP falls before or coincident with HR.
> Type 3: vasodepressor. HR does not fall >10% from maximum rate during tilt. Fall in BP precipitates syncope.

A positive orthostatic response was defined by symptoms of syncope or near-syncope with a drop in systolic BP >20 mm Hg and/or an increase in HR >20 bpm.

For statistical analysis all means are presented with standard deviations. Additional variables were assessed using χ^2 or Fisher exact tests as appropriate for categorical variables and *t* tests for continuous ones.

Results

Seventy-four patients were identified for this study. The mean duration of CRPS was 6.5 ± 4.6 years with an average pain intensity of 7.7 ± 1.4 on a 0–10 scale. All patients had localized severe pain, whereas 29 (39.2%) patients also experienced severe pain throughout their entire body. The majority (54 patients, 73.0%) had an initial injury to their upper body. There were no significant abnormalities identified on the 12-lead ECG or on the 2-D echocardiograms of the CRPS patients. One patient had a bicuspid aortic valve, but had no significant aortic regurgitation. Heart rate variability (HRV) by time domains on 24-hour Holter monitoring was normal for all subjects.

The demographics of the study patients are presented in Table 1. Among the CRPS patients, 28 (37.8%) reported pretest symptoms of syncope or presyncope. Eight CRPS patients (10.8%) were unable to complete the HUTT due to severe pain. Twenty-eight of 66 patients with CRPS (42.4%) who completed the HUTT had an abnormal test due to hemodynamic changes associated with syncope or near-syncope as classified by the VASIS criteria (Table 2). The 28 CRPS patients who had a positive HUTT were classified as follows: (1) 17 (60.7%) type 1 (mixed response), (2) 1 (3.6%) type 2A (cardioinhibitory without asystole), (3) 2 (7.1%) type 2B (cardioinhibitory with asystole), (4) 3 (10.7%) type

Table 1. Characteristics of the Study Patients (N = 74)

	CRPS Patients, No. (%)
Mean age, y [SD]	43.2 [14.0]
Female gender	63 (85.1)
Unable to complete tilt table due to pain	8 (10.8)
Positive tilt table (of completers)	28 (42.4)
Unprovoked positive	4 (14.3)
Pretest symptoms	
No symptoms	46 (62.2)
Only presyncopal symptoms	10 (13.5)
Any syncopal symptoms	18 (24.3)
During HUTT	
Mean maximum heart rate [SD]	111.3 [21.8]
Mean maximum SBP [SD]	128.0 [15.9]
Mean maximum DBP [SD]	83.8 [9.9]
Mean heart rate — Holter monitor	82.5 (10.1)
Abnormal 2-D echocardiogram	1/56 (1.8%)

Abbreviations: 2-D, 2-dimensional; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

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Table 2. Vasovagal Syncope International Study Categorization for Subjects With a Positive Head-Up Tilt Table Test (n = 28)

VASIS Criteria	CRPS Subjects With a Positive HUTT, No. (%)
Type 1: mixed	17 (60.7)
Type 2A: cardioinhibitory without asystole	1 (3.6)
Type 2B: cardioinhibitory with asystole	2 (7.1)
Type 3: vasodepressor	3 (10.7)
Orthostasis	5 (17.9)

Abbreviations: CRPS, complex regional pain syndrome; HUTT, head-up tilt table test; VASIS, Vasovagal Syncope International Study.

3 (vasodepressor response), and (5) 5 (17.9%) experienced symptoms of syncope or near syncope with an orthostatic response (a drop in systolic BP >20 mm Hg and/or an increase in HR >20 bpm). In each of these 5 patients with an orthostatic response, their systolic blood pressure fell to <90 mm Hg (range, 86–58 mm Hg), and all had symptoms of presyncope or syncope.

The majority of CRPS patients who had a positive HUTT (23 patients, 82.1%) required nitroglycerine provocation. Four patients (14.3%) had a positive HUTT during the passive phase of the HUTT without nitroglycerin provocation, and 1 patient (3.6%) had a positive HUTT with Isuprel. Among CRPS patients, there was no association between specific pain characteristics, duration, or severity of symptoms and a positive HUTT. However, those patients with lower limb involvement were more likely to be positive on HUTT (Table 3) as were younger compared to older CRPS patient. The presence of any pretest syncopal symptoms was nearly twice as high among CRPS with a positive HUTT compared to those with a negative HUTT, but this association did not reach statistical significance (Table 3).

Data from 24-hour monitoring showed no significant difference in HRV assessed by time domains between CRPS patients with and without positive HUTT.

Discussion

To our knowledge this is the first study to recognize that symptoms of presyncope and syncope are common in patients with CRPS. In our study almost 40% of patients complained of symptoms of presyncope and syncope. Furthermore, we demonstrated a high prevalence of neurocardiogenic syncope with almost one half of the study population having a positive HUTT. None of the patients were found to have any structural heart disease or arrhythmic events that may have explained their symptoms of presyncope and syncope. Ours is the first study to demonstrate this enhanced predisposition to neurocardiogenic syncope during head-up tilt table testing in patients with CRPS.

This enhanced predisposition to neurocardiogenic syncope is due to autonomic dysfunction, which is a cardinal feature of CRPS. The absence of an appropriate

Table 3. Comparison of Clinical Characteristics of Patients With Positive and Negative Head-Up Tilt Table Test (n = 66)

	CRPS Patients		
	Negative HUTT, No. (%)	Positive HUTT, No. (%)	*P* Value
Mean age, y [SD]	46.3 [13.2]	37.2 [12.8]	0.007
Female gender	32 (84.2)	25 (89.3)	0.55
Pretest symptoms			
No symptoms	26 (68.4)	15 (53.6)	0.29
Only presyncopal symptoms	6 (15.8)	4 (14.3)	
Any syncopal symptoms	6 (15.8)	9 (32.1)	
Mean duration CRPS, y [SD]	6.8 [4.4]	5.1 [3.6]	0.1
Mean pain intensity on 1–10 scale [SD]	7.6 [1.3]	7.7 [1.5]	0.78
Initial injury site			
Upper body	32 (84.2)	16 (57.1)	0.015
Lower body	6 (15.8)	12 (42.9)	
Generalized to total body	17 (44.7)	7 (25.0)	0.1

Abbreviations: CRPS, complex regional pain syndrome; HUTT, head-up tilt table test; SD, standard deviation.

reflex-induced increase in heart rate as blood pressure falls, especially after administration of a vasodilator, is a manifestation of autonomic dysfunction. The mechanism of impaired autonomic reflexes as applied to the central circulation may be similar to that delineated in the peripheral circulation.[4–8,12–16] These may include failure of efferent sympathetic vasoconstriction, absent or ineffective somatosympathetic reflexes, or deficient sympathetic innervation to the heart. CRPS patients with lower limb involvement were more likely to have vasovagal syncope or orthostasis on HUTT than those with upper extremity or total body involvement. Catecholamine hypersensitivity in CRPS results in downregulation of sympathetic outflow, which results in impaired vasoconstriction in the affected limb or limbs.[4,5] Autonomic dysregulation in the lower extremities may result in venous pooling as a result of impaired sympathetic vasoconstriction, which may partly account for the enhanced predisposition to a positive HUTT.

A limitation of our study is the lack of a healthy control group. However, previous reports estimate the prevalence of a positive HUTT among healthy individuals to be between 3% and 25%, which averages to a positive HUTT rate of approximately 10% (Table 4).[17–20] In our study, the prevalence of a positive HUTT was significantly higher and almost 5 times higher than reported for otherwise healthy individuals. In addition, we evaluated patients with severe symptoms of CRPS, and our findings may not apply to CRPS patients with just mild symptoms.

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Table 4. Comparison of Head-Up Tilt Table Result From Our Chronic Regional Pain Syndrome Subjects and Normal Controls From the Literature

Source	Total	Female, No. (%)	Mean Age (SD)	Positive HUTT, No. (%)
Grubb et al[18]	34	13 (38.2)	33 (1.7)	1 (2.9)
Podoleanu et al[19]	16	9 (56.3)	26 (6.5)	4 (25.0)
Aerts et al[17]	18	3 (16.7)	26 (6.0)	3 (16.7)
Radrigan et al[20]	21	7 (33.3)	26 (3.5)	1 (4.8)
Total controls	89	32 (36.0)	27.8 (9.7)	9 (10.1)
CRPS patients in our study	74	63 (85.1)[a]	43.2 (14.0)[a]	33 (45.2)[a]

Abbreviation: HUTT, head-up tilt table.
[a] $P < 0.001$ for chronic regional pain syndrome (CRPS) patients compared to total normal controls.

Conclusion

Patients with CRPS often have symptoms of presyncope and syncope that are related to the autonomic dysfunction, which is a cardinal feature of this chronic pain syndrome. The autonomic dysregulation responsible for the peripheral manifestations of this syndrome may predispose these patients to neurocardiogenic syncope via impaired sympathetic vasoconstriction and venous pooling, especially in CRPS patients with lower limb involvement. Patients with CRPS may often be referred to a cardiologist for symptoms of presyncope or syncope. Physician awareness of this syndrome will lead to improved recognition and treatment of CRPS patients with complaints of presyncope or syncope. Further investigation is warranted to assess whether adequate pain management will improve the autonomic dysfunction associated with the syndrome.

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